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SYSTEMATIC REVIEWS

Novel understanding of ABC transporters ABCB1/MDR/P-glycoprotein, ABCC2/MRP2, and ABCG2/BCRP in colorectal pathophysiology

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Abstract

AIM: To evaluate ATP-binding cassette (ABC) transporters in colonic pathophysiology as they had recently been related to colorectal cancer (CRC) development.

METHODS: Literature search was conducted on PubMed using combinations of the following terms: ABC transporters, ATP binding cassette transporter proteins, inflammatory bowel disease, ulcerative, colitis, Crohns disease, colorectal cancer, colitis, intestinal inflammation, intestinal carcinogenesis, ABCB1/P-glycoprotein (P-gp/CD243/MDR1), ABCC2/multidrug resistance protein 2 (MRP2) and ABCG2/breast cancer resistance protein (BCRP), *Abcb1/Mdr1a*, *abcc2/Mrp2*, *abcg2/Bcrp*, knock-out mice, tight junction, membrane lipid function.

RESULTS: Recently, human studies reported that changes in the levels of ABC transporters were early events in the adenoma-carcinoma sequence leading to CRC. A link between ABCB1, high fat diet and gut microbes in relation to colitis was suggested by the animal studies. The finding that colitis was preceded by altered gut bacterial composition suggests that deletion of *Abcb1* leads to fundamental changes of host-microbiota interaction. Also, high fat diet increases the frequency and severity of colitis in specific pathogen-free *Abcb1* KO mice. The *Abcb1* KO mice might thus serve as a model in which diet/environmental factors and microbes may be controlled and investigated in relation to intestinal inflammation. Potential molecular mechanisms include defective transport of inflammatory mediators and/or phospholipid translocation from one side to the other of the cell membrane lipid bilayer by ABC transporters affecting inflammatory response and/or function of tight junctions, phagocytosis and vesicle trafficking. Also, diet and microbes give rise to molecules which are potential substrates for the ABC transporters and which may additionally affect ABC transporter function through nuclear receptors and transcriptional regulation. Another critical role of ABCB1 was suggested by the finding that ABCB1 expression identifies a subpopulation of pro-inflammatory Th17 cells which were resistant to treatment with glucocorticoids. The evidence for the involvement of ABCC2 and ABCG2 in colonic pathophysiology was weak.

CONCLUSION: ABCB1, diet, and gut microbes mutually interact in colonic inflammation, a well-known risk factor for CRC. Further insight may be translated into preventive and treatment strategies.

Key words: ATP-binding cassette transporters; Colorectal cancer; Intestinal; Inflammatory bowel disease; Inflammation; Adenoma-carcinoma sequence

Core tip: Recently, human studies reported that changes in the levels of ATP-binding cassette (ABC) transporters were early events in the adenoma-carcinoma sequence leading to colorectal cancer. A link between ABCB1, high fat diet and gut microbes in relation to colitis was suggested by the animal studies. The *Abcb1* KO mice might thus serve as a model in which diet/environmental factors and microbes may be controlled and investigated in relation to intestinal inflammation. Such strategy may provide insight which can be translated into preventive and treatment strategies to benefit the patients.

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INTRODUCTION

Colorectal cancer (CRC) constitutes the third most common cancer in the world and the second leading cause of cancer-related deaths. The number of cases is increasing and has been estimated to raise from 1.4 million cases in 2012 to 2.4 million cases in 2035 worldwide[1]. Early detection of CRC is important as early treatment has been associated with improved outcomes and saved lives[2]. Therefore, population screening programs have been initiated in a number of countries such as the United Kingdom, Australia, Holland and Denmark[3-6]. The fecal occult blood test (FOBT) is the most widely used for population screening[7] and individuals with a positive FOBT are referred for an endoscopic investigation of the colonic mucosa thereby enabling the sampling of biopsies from the colonic mucosa.

Recently, a major part of research had focused on improving prognosis and treatment selection in CRC[8-10]. Another approach could be to prevent the development of cancer in subgroups of patients with high risk, *i.e.,* secondary prevention. Thus, the molecular evaluation of the (unaffected) colonic mucosa from the patients undergoing an endoscopic evaluation could potentially stratify the patients according to their risk of developing CRC. Our recent findings indicate that even healthy looking mucosa as determined by histology may contain a significantly elevated level of immune response proteins[11]. Biomarkers potentially predicting the disease risk among selected patient groups could improve the efficiency of the screening programs and patient care. Furthermore, they have the potential to dramatically alter the established patient care pathways as follow-up of the patients may be tailored according to their individual risk and thereby the organization and use of resources of the health care system.

CRC develops in the colonic mucosa which is highly affected by the metabolic activities in the intestinal lumen. The dietary items reaching the colon are digested by the commensal bacteria giving rise to various substrates which may prevent, initiate or promote colorectal cancer development[12]. Thus, in order to understand the processes leading to CRC we need to take into account the delicate interactions between dietary intake, activity of the commensal bacteria and host factors.

We recently reported that low *ABCB1* and *ABCG2* gene transcription levels and high *ABCC2* levels are early events in the colorectal adenoma-carcinoma sequence[13,14] suggesting that changes in expression levels of the ATP binding cassette (ABC) transporter proteins [EC 3.6.3.44] precede cancer development. In addition, inflammatory bowel disease (IBD) may be a risk factor for the development of CRC[8]. Therefore, we wanted to discuss the current understanding of how these ABC transporters may affect intestinal inflammation and carcinogenesis, how they may potentially interact with the environment such as diet and gut microbes, and whether this knowledge may be utilized for improved treatment care strategies.

MATERIALS AND METHODS

Literature search was conducted on PubMed using combinations of the following terms: ABC transporters, ATP binding cassette transporter proteins, inflammatory bowel disease, ulcerative, colitis, Crohn's disease, colorectal cancer, colitis, intestinal inflammation, intestinal carcinogenesis, ABCB1/P-glycoprotein (P-gp/CD243/MDR1), ABCC2/multidrug resistance protein 2 (MRP2) and ABCG2/breast cancer resistance protein (BCRP), A*bcb1/Mdr1a*, *abcc2/Mrp2*, *abcg2/Bcrp*, knock-out mice, tight junction, membrane lipid function.

RESULTS

ABC family of transporters; ABCB1, ABCC2, and ABCG2

The large family of ABC transporter proteins is highly conserved through evolution and extensive sequence and protein homology is shared between numerous bacterial and eukaryotic ABC transport proteins[15]. The ABC proteins are found in the cell membranes and intracellular organelles and the ABC family members exert multiple different functions depending on the cellular context[16].

The ABCB1, ABCC2, and ABCG2 transporters, encoded by *ABCB1*, *ABCC2*, and *ABCG2,* respectively, are located in the apical cell membrane of epithelial and endothelial interfaces within the intestine, testis, kidneys, liver, brain, and placenta[17-20]. Thereby, they exert barrier functions influencing absorption, distribution, excretion, and toxicology (ADME-Tox) of exogenous substrates with potential impact on inflammation and carcinogenesis[21-25]. ABCB1 and ABCG2 transporters have also been identified on haematological cells[20,26,27]. Whereas ABCB1 has been extensively studied in relation to the gastrointestinal system[28], less is known for ABCC2 and ABCG2[29].

No monogenic diseases have been identified involving *ABCB1* and *ABCG2*[30,31], but several different mutations in *ABCC2* have been observed in patients with Dubin-Johnson syndrome, an autosomal recessive disorder characterized by conjugated hyperbilirubinemia[32].

Nuclear receptors such as aryl hydrocarbon receptor (AHR), pregnane x receptor (PXR, NR1I2), vitamin D receptor (VDR, NR1I1), and constitutive androstane/activated receptor (NR1I3) are activated by a wide variety of exogenous and endogenous factors including diet, heavy metals, gut microbes, carcinogens and inflammation[33,34] (reviewed in[35]). These nuclear receptors may be involved in the transcriptional regulation of ABC transporters[34,36-40] as are the transcription factors nuclear factor kappa B (NF-κB), activator protein 1 (AP-1)[41], and Wnt signaling transcription factor TCF4[42]. Furthermore, ABCB1 undergoes several posttranslational modifications (PTMs)[43,44] which have been shown to affect the stability of ABCB1 and/or substrate transport specificities[45]. ABCB1 is a 170-180 kDa glycoprotein with N-linked glycosylation at residues Asp[91], Asp[94] and Asp[99]. ABCB1 and ABCC2 have two ATP-binding sites and two six-transmembrane domains in a symmetric structure whereas ABCG2 is a half-transporter and have one ATP binding site and one six-transmembrane domain.

ABC transporter substrates include many diverse endogenous and exogenous molecules including amino acids, peptides, metabolites, vitamins, fatty acids, steroids, phospholipids, conjugated organic anions, and dietary and environmental carcinogens, pesticides, metals, metalloids, lipid peroxidation products and drugs[22-24]. Substrate overlap has been reported between the ABCB1, ABCC2, ABCG2, and especially between ABCC2 and the basolaterally located ABCC1[23,29]. Specific substrates and their potential role in ABC transporter related gut inflammation will be discussed later in this review.

Inflammation is a key factor underlying the development of CRC

CRC is a heterogeneous disease complex with environmental, genetic and host factors involved in the aetiology[46,47]. Inflammation is a risk factor for CRC[48-50] and accordingly, a subset of patients with IBD[51,52] [with the two main forms ulcerative colitis (UC) and Crohn's disease (CD)] characterised by long-term and extensive colitis are at high risk of CRC[53,54]. The incidences of both CRC and IBD are rising[1,55], which point to important roles of environment factors.

The intestinal mucosa is by far the body's largest surface exposed to and interacting with environmental factors. The intestinal epithelium and the mucus form a barrier against luminal antigens and invading microbes[56,57]. Microbial sensing by intestinal epithelium cells and local innate lymphoid cells (ILCs) through pattern recognition receptors (PRR) leads to secretion of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interferon-γ (INF-γ), interleukin 6 (IL-6), and IL-17[58,59], cytokines which have been related to IBD and CRC[60]. Activation of PRR stimulates autophagocytic networks[61,62]. Also, activation of the innate immune system may result in activation of the adaptive immune response with T cell involvement; Th1, Th2 and Th17 cells characterised by secretion of their signature cytokines INF-γ, IL-4, IL-17, respectively, whereas Tregs (and to a lesser degree Th2), in contrast, are characterised by their production of the anti-inflammatory cytokines IL-10 and transforming growth factor β (TGF-β)[63,64]. The

Table 1 The *ABCB1*, *ABCC2* and *ABCG2* mRNA and protein levels in intestinal tissue from patients with ulcerative colitis

		Controls	Inactive disease				Active disease				Ref.
		Colon	Colon	*P* value	Rectum	*P* value	Colon	*P* value	Rectum	*P* value	
Gene	*ABCB1*[1]	1 (ref)	NA	NS	NA		22%	< 0.001	34%	< 0.01	[72]
	ABCC2[1]	1 (ref)	NA	NS	NA		NA	NS	NA	NS	[72]
	ABCG2[1]	1 (ref)	NA	NS	NA		11%	< 0.001	16%	< 0.001	[72]
Array	*ABCB1*[2]	287	-1.5								[40]
	ABCC2[2]	81	-8.6								[40]
Protein	ABCG2[3]	100 (9/9)	80 (53/67)				24 (13/54)	0.01			[73]

[1]The *ABCB1*, *ABCC2* and *ABCG2* mRNA levels in colon and rectum tissue from patients with ulcerative colitis in remission (n = 17) or with active disease (n = 16) compared to the levels in colon tissue from healthy controls (n = 17). mRNA levels are normalised to the villin mRNA level. *P* values compared to the expression in the controls; [2]Microarray analyses of pooled cRNA from uninflamed colonic tissue from 4 patients with UC and 4 control subjects. Fold change expression in colon tissue compared to controls. Statistically significant expression levels of *ABCB1* were found in UC patients compared to controls by RT-PCR analyses using 18S RNA as internal control (P < 0.05); [3]Quantitative immunohistochemistry of formalin-fixed paraffin-embedded (FFPE) colonic biopsies from 9 healthy individuals and 36 patients with ulcerative colitis. The values are n % (samples with positive staining/total number). *P* value for active colitis compared to controls and inactive colitis, respectively. NA: Not available; NS: Not significant.

role of the Th17-associated cytokines in animal models of colitis[65], IBD[66] and CRC[67] have been in focus the recent years and it has been suggested that Th17 cells may have evolved to combat bacterial and fungal infections *via* orchestration of the neutrophil inflammatory response[63]. However, this seems to be a simplistic view[68] and more T cell subsets with as yet unclarified functions in IBD and CRC have been identified these years[69-71].

ABC transporters, IBD and CRC

Englund *et al*[72] found significantly lower levels of both *ABCB1* and *ABCG2* mRNA in colon and rectal biopsies from 16 patients with active UC compared to healthy individuals whereas the levels did not differ between UC patients in remission and healthy controls (Table 1). The authors also reported lower ABCB1 and ABCG2 levels in colon from patients with active inflammation compared with controls[72]. Langmann *et al*[40] reported low levels of *ABCB1* and *ABCC2* mRNA in biopsies from colon adjacent to inflammation from patients with UC compared to the levels in controls. In contrast, Deuring *et al*[73] reported similar levels of *ABCG2* mRNA in intestinal biopsies from healthy individuals, patients in remission and patients with active inflammation but dramatically reduced levels of ABCG2 in IBD patients with active inflammation when compared to patients in remission or healthy controls using quantitative immunohistochemistry (Table 1). These observations suggest that the low levels of ABCG2 observed in inflamed colon were caused by posttranscriptional processes[73]. The study also found inflamed colon to contain high levels of the endoplasmic reticulum (ER)-stress marker GRP78 and *in vitro* they found nitric oxide induced ER-stress to impair ABCG2 function[73]. The authors therefore suggested that incorrect protein folding caused by inflammation-induced ER dysfunction may lead to low levels of ABCG2 in inflamed colon of IBD patients[73,74].

The role of ABC transporters has also been investigated in relation to CRC (Table 2). As previously mentioned, low levels of *ABCB1* in colon was found to be an early event that preceded malignancy[13]. Similarly, in another study using the same cohort low levels of *ABCG2* and high levels of *ABCC2* mRNA were found in both colon adenomas and carcinomas compared to morphological normal tissue surrounding the cancer tissue, and compared to levels in tissue from healthy individuals[14]. Taken together, the studies suggest that changed expression levels of the ABC transport proteins may be early events in the development of IBD and CRC.

Genetically determined variation in ABC transporters has been investigated in relation to risk of developing IBD[75-79] and CRC[80-82] with varying results[83-85]. In particular the polymorphisms *ABCB1* C1236T, G2677T/A, and C3435T have been investigated. These polymorphisms are in linkage disequilibrium. Haplotype frequencies vary among ethnic groups and the CGC and TTT haplotypes are frequent among Caucasians[86]. The synonymous C3435T polymorphism was reported to cause changes in protein folding due to ribosome stalling caused by impaired interaction between the tRNA and the chaperone protein that aids the folding process at the ribosome[86] which resulted in altered transporter function[87]. A recent meta-analysis found that the *ABCB1* C3435T polymorphism (rs1045642) was associated with risk of UC, but not with CD[84]. In relation to CRC, a large case-control analysis of a Czech and two German cohorts of 4677 cases in total found no indications of a strong role of *ABCB1* in CRC[88] which was in accordance with a meta-analysis (not including the above study)[85]. A prospective study based on a Danish cohort found that two *ABCB1* polymorphisms, including the C3435T polymorphism, were associated with CRC risk[82]. Furthermore, these two polymorphisms were found to interact with meat intake in relation to risk of CRC. Only few studies of *ABCC2* and *ABCG2* polymorphisms as risk factors for IBD and CRC have been performed. No strong indications that genetic variation in *ABCC2* or *ABCG2 per see* is associated with IBD or CRC were

Table 2 The *ABCB1*, *ABCC2* and *ABCG2* mRNA levels in intestinal tissue from patients with adenomas and colorectal cancer and healthy individuals

	Unaffected tissue	*P* value[1]	Adenomas/carcinomas	*P* value[1]	*P* value[2]	Ref.
ABCB1						[13]
Healthy individuals	0.012 ± 0.008					
Mild/moderate dysplasia cases	0.009 ± 0.004	NS	0.005 ± 0.004	< 0.050	< 0.001	
Severe dysplasia cases	0.009 ± 0.030	NS	0.003 ± 0.002	< 0.050	< 0.001	
Cancer patients	0.009 ± 0.014 (distant)	< 0.05	0.003 ± 0.005	< 0.001	< 0.001	
	0.007 ± 0.009 (adjacent)	< 0.05			< 0.010	
ABCC2						[14]
Healthy individuals	5.35 ± 3.24					
Mild moderate dysplasia cases	4.62 ± 4.79	0.081	6.68 ± 6.77	0.87	0.037	
Severe dysplasia cases	6.66 ± 8.47	0.880	10.18 ± 11.52	0.27	0.240	
Cancer patients	28.06 ± 68.84 (distant)	0.036	87.50 ± 270.21	0.0046	0.0037	
	11.44 ± 25.58 (adjacent)	0.690			< 0.0001	
ABCG2						[14]
Healthy individuals	718.06 ± 761.24					
Mild moderate dysplasia	732.85 ± 2305.28	0.550	56.02 ± 118.42	< 0.0001	< 0.0001	
Severe dysplasia	448.02 ± 195.34	0.840	76.31 ± 102.63	< 0.0001	< 0.0001	
Cancer patients	6679 ± 58353 (distant)	0.080	98.41 ± 476.36	< 0.0001	< 0.0001	
	1302 ± 10090 (adjacent)	0.011			< 0.0001	

[1]*P* values for comparison of the expression levels in tissue from healthy individuals adjusted for age and gender. Samples were available for 18 healthy controls, 88-94 patients with mild/moderate dysplasia, 12 with severe dysplacia, and 121-122 patients with CRC; [2]*P* value for the comparison of the expression levels in morphologically unaffected and affected tissue from the same individual using Paired Student's *t*-test. All values are mean ± SD. *ABCB1* mRNA levels are normalised to the *β-actin* mRNA level. *ABCC2* and *ABCG2* mRNA levels are normalised to 18S RNA levels. Matching samples were available from ABCG2: 66-75 cases with mild-moderate dysplasia, 11 cases with severe dysplasia, and 63-80 and 66-99 CRC cases (distant unaffected tissue, and adjacent unaffected tissue, respectively). NS: Not significant.

found[80,81].

ABC transporters and colitis and dysplasia in animal models

The *Abcb1/Mdr1a* knock-out (*Mdr1a* KO) mouse, in which the gene corresponding to the human intestinal *ABCB1* gene has been deleted[89,90], has been utilized as an animal model of colitis[91-95]. The colitis is characterized by histological changes and high levels of the cytokines INF-γ, TNF-α, IL-1β, IL-6 and IL-17 thus resembling the findings in UC patients. The classical study by Panwala *et al*[91] reported that a proportion of *Mdr1a* KO mice developed colitis when exposed to commensal gut bacteria. The development of spontaneous colitis was prevented if the mice were maintained germfree. Also, spontaneous colitis and active inflammation was resolved by oral treatment with a mixture of streptomycin, neomycin, bacitracin, and amphotericin. These findings highlight an important role of bacteria in the initiation and perpetuation of colitis in the *Mdr1a* KO mouse[91]. Since then, the finding that lack of *Mdr1a* confers risk of colitis has been replicated by others[94-98]. Furthermore, a proportion of the *Mdr1a* KO mice dual-infected with Helicobacter species (*H.bilis* and *H. hepaticus*) developed dysplasia[99].

One study found redused in the diversity and total number of bacteria in *mdr1a* KO mice compared to wildtype mice. These alterations were found to precede and associate with the development of inflammation[95]. Another study reported changes in colonic gene expression which also preceded disease development[98]. High expression of INF-γ was found in histologically normal colonic tissue from *Mdr1a* KO mice and the change preceded a high expression of the inflammatory cytokines IL-1β, IL-6, TNF-α, increased colonic permeability, and histologically determined colon inflammation[98]. Yet, another study found a high level of the pro-inflammatory cytokine IL-17 in colon from the *Mdr1a* KO mice model[92]. INF-γ expression has been associated with reduced intestinal barrier function due to effects on tight junction proteins[96]. Also, one study suggested that impaired intestinal barrier function contributed to the development of colitis in *Mdr1a* KO mice. In this study, high permeability of FITC-dextran (4.4 kDa) and horseradish peroxidase (44 kDa) was found in colon tissue mounted in Ussing chambers and *in vivo*, high bacterial translocation to lymphoid tissue including increased trabecular infiltrate with neutrophils were found[94]. These changes were observed prior to onset of colitis. Furthermore, decreased phosphorylation of tight junction proteins including occludin was observed[94]. Thus, inflammation and the following high INF-γ expression may contribute to the loss of barrier function which has been observed in the *Abcb1* KO mice.

High fat diet-induced obesity increases the frequency and severity of colitis in the *mdr1a* KO mice[100]. Wildtype mice feeding either high-fat diet or low fat diet did not develop colitis[100]. In contrast, specific pathogen free *Mdr1a* KO mice fed high fat diet had a higher frequency and more severe colitis compared to those who were fed a low fat diet[100]. Although

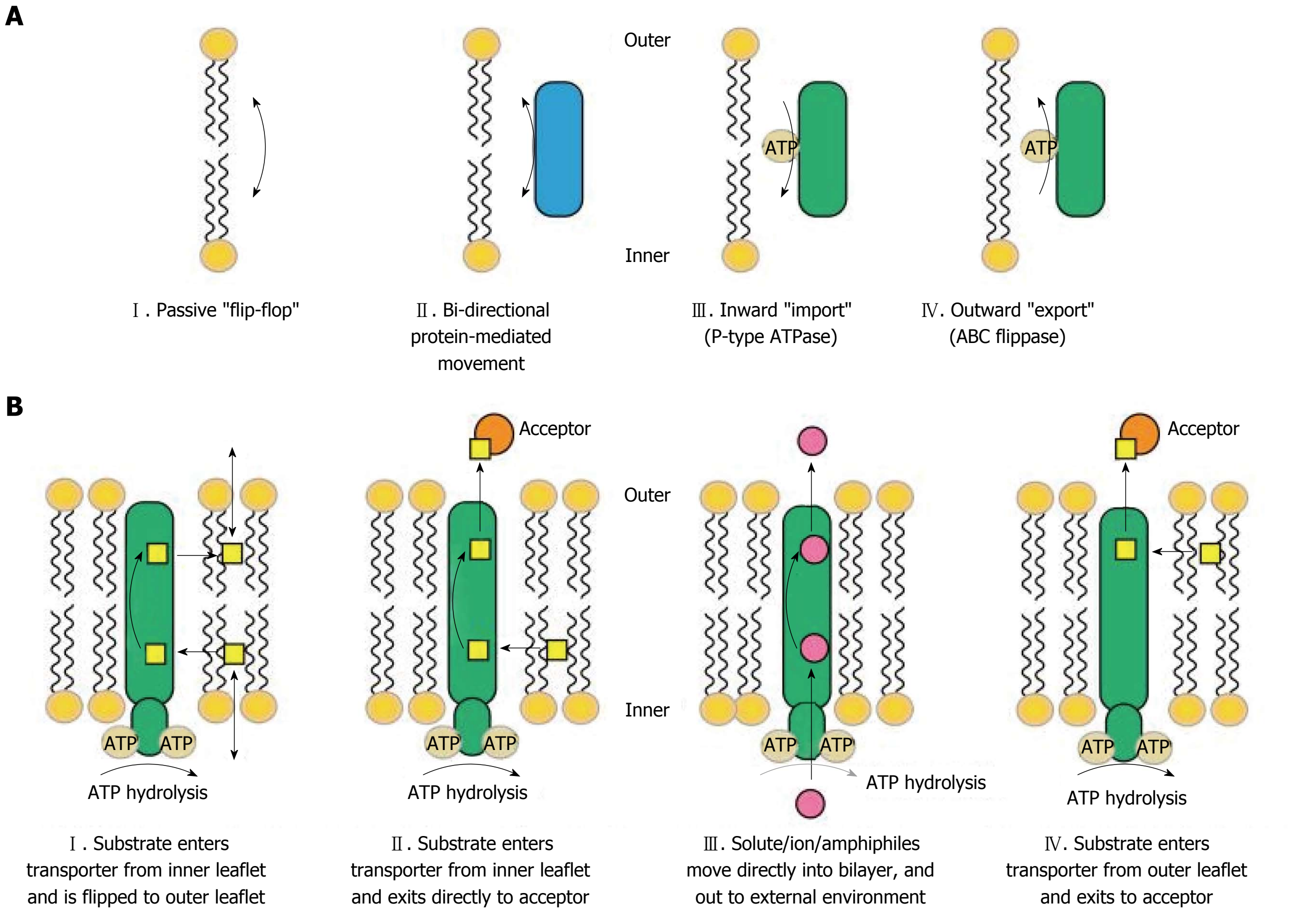

Figure 1 The models presented are from Tarling *et al*[16]. A: Lipids can move across the membrane bilayer by multiple mechanisms. Four mechanisms are proposed here: (1) membrane lipids passively diffuse or "flip-flop" from one leaflet of the bilayer to another; (2) bi-directional movement of lipids from one membrane leaflet to another is enhanced by proteins present in the membrane bilayer; (3) P-type ATPases mediate the movement of specific lipids (phospholipids) from the outer leaflet of the membrane bilayer; and (4) ABC transporters/flippases mediate the "outward" movement of specific lipids (phospholipids/cholesterol) from the inner leaflet to the outer leaflet of the membrane bilayer; B: Mechanisms of substrate recognition and transport by ABC transport proteins: (1) substrates enter the transporter from the inner leaflet and are flipped to the outer leaflet where they can exit the membrane bilayer; (2) as in (1) but the substrate exits the transporter directly to an exogenous acceptor; (3) solute/ions/amphiphiles move directly into the bilayer, through the transporter protein and out to the external environment; and (4) substrates enter the transporter from the outer leaflet and exits to an acceptor molecule.

the microbiota was not investigated in this study, the authors concluded that the diet and potential diet-induced changes in microbiota was not sufficient to induce colitis in the mice but that additional host genetic factors are required before the high fat diet is a risk factor for colitis[100].

Impaired immune system may also be involved in the aetiology of colitis in the *Mdr1a* KO mice model. In mice, regulatory T cells (Tregs) characterised by the expression of the transcription factor Foxp3[101] are considered to down-regulate effector T cells that react to microbial or other gastrointestinal antigens. In the study by Tanner *et al*[97], they also found that there appeared to be fewer Tregs present in intestine from *mdr1a* KO mice and that these Tregs were unable to effectively suppress TNF-α induced colitis. These results are in accordance with the notion that inflammation primarily is initiated by the innate immune system.

In contradiction to the findings in the *Mdr1a* KO mice model, *Abcc2/Mrp2* KO and *Abcg2/Bcrp1* KO mice were found to be phenotypically normal under standard housing conditions[102,103].

The molecular mechanisms of ABC transporters may involve phospholipid transport

Cellular processes such as phagocytosis, apoptosis, cytokine release, vesicle formation and tight junction function require cell membrane budding and curvature and therefore, different composition of the inner and outer side of the lipid bilayer forming the cell membrane (Figure 1)[104]. Translocation of phospholipids between the two sides of the lipid bilayer within the cell membrane is therefore important for generating such differences. ABCB1, ABCC2, and ABCG2 have been found to translocate various phospholipid membrane components; cholesterol, sphingomyelin, and other glycosphingolipids suggesting that ABC transporters are important for regulating the budding of the membrane function[15,16,105,106]. Furthermore, the cellular processes also require cell cytoskeleton anchoring through specialised domains[107]. ABCB1 has been found to be associated with such domains[106,108,109]. Other phospholipid transporters such as scramblases, P4-ATPases and additional members of the ABC transporter family, are reviewed in[15].

In vitro studies of rat kidney and Sertoli cells support the involvement of ABC transporters in tight junction function and apoptosis[110,111]. At the Sertoli cell blood-testis barrier, ABCB1 was found to co-localise with occluding, claudin-11 and junction adhesion molecule A[110]. Knockdown of *Abcb1* (*Abcb1a* and *Abcb1b*) by RNAi in rat Sertoli cell cultures led to a decline of claudin-11, internalisation and degradation of occluding, and disruption of tight junction barrier function[110]. Another study found that ABCB1 decreased apoptosis by decreasing the availability of a precursor of ceramide[111], an intracellular signalling molecule involved in apoptosis induced by TNF-α and other apoptotic stimuli[106,108]. However, the functions of the ABC transporters may be tissue specific and therefore the results may not apply for intestinal conditions.

The molecular mechanisms of ABC transporters may be related to the transport of other substrates

Figure 1 shows mechanisms of substrate recognition and transport by ABC transporters[16]. An *in vitro* study by Pawlik *et al*[112] on cultured peripheral blood mononuclear cells PBMC from healthy individuals found that stimulation with phytohaemagglutinin (PHA) leads to secretion of IL-2, IL-4, IL-6, IL-10, INF-γ, and TNF-α[112]. Furthermore, secretion of IL-2, IL-4, INF-γ, and TNF-α was inhibited by anti-MDR1 specific antibody whereas secretion of IL-6 and IL-10 was unaffected. In a similar study, blockade of ABCC1 by anti-MRP1 specific antibodies led to reversible abrogated cytokine secretion of IL-10, TNF-α, IL-4 and INF-γ[113]. However, another study using splenocytes from *Mdr1a* KO mice found that IL-2, IL-4, IL-10, and INF-γ secretion was independent of ABCB1. The authors suggested that ABCB1 may not be required for secretion of these cytokines because they contain a signal sequence designating the cytokines for secretion from the cells[114]. Yet, a further *in vitro* study by Pawlik *et al*[115] on cultured PBMC, this time from 72 healthy *ABCB1* genotyped individuals was conducted. The cultured cells were stimulated with PHA and cytokines were measured in the supernatant. The authors found significantly lower concentration of IL-2, IL-4, INF-γ, and TNF-α, and unchanged concentration of IL-6 and IL-10 in cultured cells from individuals with *ABCB1* C3435T TT genotypes compared to CC genotypes[115]. Also, ABCB1 blockade by the antagonist PSC833 resulted in impaired IL-12 secretion by antigen presenting cells from peripheral blood from healthy human volunteers suggesting that functional ABCB1 is required for IL-12 secretion in these cells[116]. As previously mentioned, cytokines and chemokines are important modulators of intestinal inflammation and carcinogenesis[108,117]. Additionally, ABCB1, ABCC2, and ABCG2 also transport bioactive lipids[15,16,105]. The levels of the ABCB1 substrate platelet-activating factor[117-119] have been found to be high in intestinal mucosa from CD patients[120]. PAF has been reported to regulate the function of tight junctions[121] and to activate human neutrophils to extrusion of neutrophil extracellular traps (NETs) mediating extracellular capture and killing of bacteria[122,123]. Also, ABCB1 has been reported to transport steroids, mineralocorticoids, androgens and oestrogens[106]. Interestingly, the ABC substrate testosterone was found to be a key mediator of autoimmune responses in the non-obese diabetic mouse model of type 1 diabetes[124]. Whether a similar phenomenon contributes to the observed male preponderance in *Mdr1a* KO IBD mouse model has not been studied as far as we know[94]. ABCG2 transport the anti-inflammatory butyrate, a product of bacterial digestion of dietary fibres, and phytoestrogen from vegetables[125,126]. ABCC2 has been reported to transport the pro-inflammatory signalling molecules leukotriene (LT) B_4 and LTC_4 involved in dendritic cell migration and CRC, and, furthermore, various diet- and smoke-derived carcinogens[127-131]. Sulfasalazine and 5-aminosalicylic acid (5-ASA, mesalazine) are used for treatment and prevention of UC flares[132]. ABCG2 is regarded as being the main transporter of sulfasalazine[133,134] and ABCG2 activity has been suggested as having impact on sulfasalazine treatment efficacy in patients with rheumatoid arthritis (RA)[135,136].

ABCB1 expression on T cells may identify pro-inflammatory Th17 cells

One study utilised ABCB1 expression to identify human Th17 cells with a unique pro-inflammatory transcriptional signature[20]. This novel subset of Th17 cells, MDR1-positive Th17 cells, was identified by fluorescence activated cell sorting (FACS) analysis of PBMC from healthy individuals. Compared to MDR1-negative Th17 cells, the MDR1-positive Th17 cells were characterized by a high production of pro-inflammatory Th1 (INF-γ) and Th17 (IL-17A, IL-17F, and IL-22) cytokines and low levels of anti-inflammatory cytokines such as IL-10 upon stimulation[20]. In contrast to the MDR1-negative T cells, the MDR1-positive T cells were resistant to treatment with glucocorticoids. Thus, MDR1-positive T cells from healthy humans were enriched two- to three-fold during culturing of peripheral blood memory T cells in the presence of glucocorticoids[20]. Furthermore, in a small study of 3-5 CD patients, MDR1-positive Th17 cells (assessed as percent of the total number of memory cells) were enriched both in non-inflamed and inflamed gut tissue compared to blood levels[20]. High mRNA levels of IFN-γ, IL23R, and TNF were found in MDR1-positive Th17 cells compared to MDR1-negative Th17 cells following FACS-sorting of mononuclear cells from gut tissue from two CD patients[20].

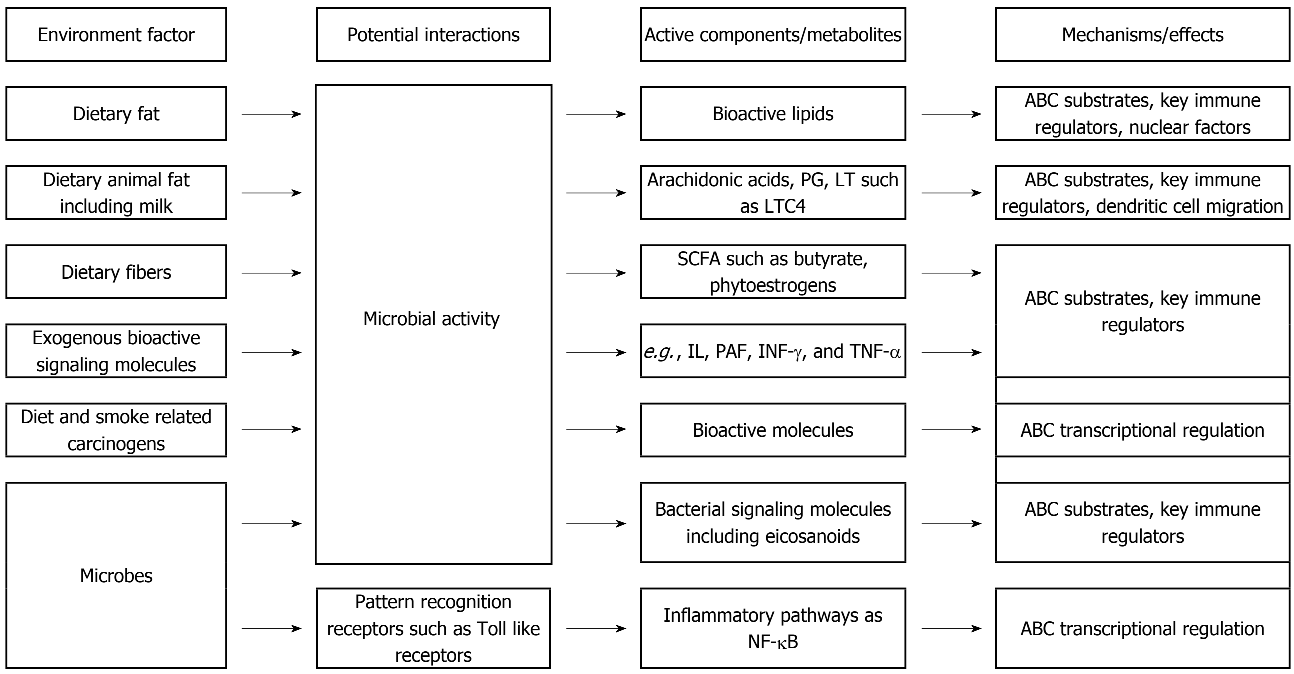

Figure 2 Proposed mechanisms for the involvement of ABC transporters in intestinal inflammation.

DISCUSSION

The ABC transport proteins may confer a link between the environment and intestinal inflammation and potentially intestinal carcinogenesis *via* intestinal inflammation[48-50,137,138] . Diet affects risk of CRC[1], the course[139-143] and risk of IBD [144-148] (reviewed in[149-153]). Diet affects gut microbial composition[154,155] and both diet and intestinal microbes affect intestinal inflammation[156,157] and carcinogenesis[12,158-161].

A link between ABCB1, diet and the gut microbes in relation to colitis is suggested by the animal studies. High fat diet increases the frequency and severity of colitis in specific pathogen-free *Abcb1* KO mice[100]. Undigested dietary items reaching the colon are digested by commensal bacteria thereby providing the host with valuable energy, essential vitamins, fatty acids etc. Dietary fibre from grains, fruit and vegetables is converted into short-chain fatty acids (SCFA) which represent important key regulators of the immune system[12]. The gut microbiome in active IBD is characterised by decreased microbial diversity with a decreased number of Firmicutes[162]. Low abundance of the *Clostridium* and *Bacteroides* species which preferentially produce butyrate and other SCFA may result in low production of SCFA[163]. High intake of meat which is a rich source of sulphur may lead to the formation of hydrogen sulphide by bacterial fermentation[12] which, at least theoretically, may be aggravated by high intake of milk fat which was found to favour the presence of the sulphate-reducing bacteria *Bilophila wadsworthia* in mice[157]. Also, intake of animal fat may give rise to arachidonic acid which is converted into *e.g.,* prostaglandins and leukotrienes[12]. Some of these molecules are ABC transporter substrates including dietary pro- and anti-inflammatory molecules, bioactive lipids, and bacterial derived molecules[125,126]. Figure 2 shows potential mechanisms of the involvement of ABC transporters in inflammation. In addition, diet and other environmental factors may impact the transcriptional regulation of ABC transporters through effects on nuclear receptors and transcription factors leading to changes of the ABC transporter activity thereby affecting IBD and CRC. The ABC transporters may impact IBD and CRC through their transport of various substrates thereby affecting underlying biological mechanisms involved in intestinal inflammation (Figures 1 and 2).

ABC transporter polymorphisms have been evaluated in relation to development of IBD and CRC with inconsistent results. These studies are based on the hypothesis that genetic variations are associated with functional changes in ABC activity and/or specificity. It has been suggested that genetic diversity of the *ABCB1* gene among various ethnicities may contribute to the varying results in candidate gene studies[164,165]. In addition, *ABCB1* polymorphisms may only be associated with risk of CRC in populations with a relevant dietary exposure[166]. This aspect may be exemplified by the finding of an interaction between meat intake and the gene *NFKB1* encoding NFκB p50 in a Danish cohort[137]. This interaction may explain the finding that the *NFKB1* polymorphism was associated with risk of CRC in a Swedish cohort but not in a Chinese cohort[167]. Meat intake are higher in Denmark and Sweden compared to China[168]. Therefore, *NFKB1* was identified as a risk gene in the Danish and Swedish high meat intake cohorts but not in the Chinese low meat intake cohort. A detailed assessment of the diet seems to be important for assessing the roles of ABC polymorphisms. Thus, future studies should focus on studying large cohorts with well-defined and relevant prospectively sampled environmental exposures in order to identify underlying IBD and CRC disease mechanisms.

Due to the many confounding parameters, potential causality cannot be evaluated through molecular epidemiological studies. Studies using animal models, where a range of parameters can be controlled are therefore needed for establishing causality. Germfree mice do not develop colitis. Although germfree mice are not exposed for living bacteria they will meet dietary derived microbial antigens which could activate PRR in the mucosa and induce inflammation. Inflammation, however, has not been observed in the germfree mice. Moreover, colitis can be prevented by antibiotics in conventionally housed, specific pathogen-free, mice. These findings suggest that microbial derived antigens are not sufficient to trigger colitis but that living microbes are needed and may thus point to potential mechanisms such as microbial derived metabolites, signalling peptides and extracellular vesicles[169,170]. Indeed, gut microbial derived metabolites were found to affect the balance between pro- and anti-inflammatory cells in mice[171]. These metabolites may be absorbed into the blood and thereby affect distant organs. Gut microbes have been reported to affect the immune system, in particular the Th17 pathway, in various autoimmune mouse models[172-176]. Some studies, but not all[177], indicate a similar mechanism in humans which might also associate with human autoimmunity[178-180]. Also, bacterially derived fatty acids and other relevant metabolites should be investigated in the *Abcb1* KO mice like it has been done in male C57BL/6 (B6) mice[171]. The *Abcb1* KO mice might provide a model, in which the interplay of environment factors, diet, and microbes can be controlled and investigated. Due to important differences of human and murine immune systems, the translational value of results obtained from the mouse model need also to be evaluated through human data.

The finding that presence of ABCB1 on immune cells could be used to identify pro-inflammatory Th17 cells may have important clinical implications as glucocorticoids are a mainstay in the treatment of serious flares of IBD[181] and since a large proportion (20%-30%) of patients are resistant to glucocorticoid treatment[182]. Thus, high ABCB1 mediated drug efflux may lead to decreased intracellular drug concentrations in target cells [183, 184] and thereby confer glucocorticoid treatment resistance. Likewise, ABCG2 activity may affect efficacy of treatment with sulfasalazine. Further evaluation of the roles of ABC transporters in treatment response in IBD is warranted.

In conclusion, results from animal and human studies indicate that ABCB1, diet, and gut microbes mutually interact in colonic inflammation. Diet and microbes may give rise to molecules which are substrates for the ABC transporters and may additionally affect ABC transporter function through *e.g.,* nuclear receptors and transcriptional regulation. The *Abcb1* KO mice might provide a model in which these factors can be controlled and investigated. Such strategy may provide insight which can be translated into preventive and treatment strategies to benefit the patients. The evidence for the involvement of ABCC2 and ABCG2 in colitis was weak.

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COMMENTS

Background

Colorectal cancer (CRC) constitutes the third most common cancer in the world and the second leading cause of cancer-related deaths. The number of cases is increasing and has been estimated to raise from 1.4 million cases in 2012 to 2.4 million cases in 2035 worldwide. Early detection of CRC is important as early treatment has been associated with improved outcomes and saved lives. Therefore, population screening programs have been initiated in a number of countries such as the United Kingdom, Australia, Holland and Denmark. The fecal occult blood test (FOBT) is the most widely used for population screening and individuals with a positive FOBT are referred for an endoscopic investigation of the colonic mucosa thereby enabling the sampling of biopsies from the colonic mucosa.

Research frontiers

Recently, a major part of research had focused on improving prognosis and treatment selection in CRC. Another approach could be to prevent the development of cancer in subgroups of patients with high risk, *i.e.,* secondary prevention. Thus, the molecular evaluation of the (unaffected) colonic mucosa from the patients undergoing an endoscopic evaluation could potentially stratify the patients according to their risk of developing CRC. Recently, human studies by authors reported that changes in the levels of ABC transporters were early events in the adenoma-carcinoma sequence leading to CRC. These findings indicate that even healthy looking mucosa as determined by histology may contain a significantly elevated level of immune response proteins.

Innovations and breakthroughs

The authors recently reported that low ABCB1 and ABCG2 gene transcription levels and high ABCC2 levels are early events in the colorectal adenoma-carcinoma sequence suggesting that changes in expression levels of the ATP binding cassette (ABC) transporter proteins [EC 3.6.3.44] precede cancer development. In addition, inflammatory bowel disease (IBD) may be a risk factor for the development of CRC. Therefore, the authors wanted to discuss the current understanding of how these ABC transporters may affect intestinal inflammation and carcinogenesis, how they may potentially interact with the environment such as diet and gut microbes, and whether this knowledge may be utilized for improved treatment care strategies. A link between ABCB1, high fat diet and gut microbes in relation to colitis was suggested by the animal studies. The Abcb1 KO mice might thus serve as a model in which diet/environmental factors and microbes may be controlled and investigated in relation to intestinal inflammation. Such strategy may provide insight which can be translated into preventive and treatment strategies to benefit the patients.

Applications

Biomarkers potentially predicting the disease risk among selected patient groups could improve the efficiency of the screening programs and patient care. Furthermore, they have the potential to dramatically alter the established patient care pathways as follow-up of the patients may be tailored according to their individual risk and thereby the organization and use of resources of the health care system.

Peer-review

Congratulations to the authors for their review on ABC transporters ABCB1/MDR/P-glycoprotein, ABCC2/MRP2, and ABCG2/BCRP in colorectal pathophysiology. It is certain that this paper will be very inspiring in this field. Personally recommend it to be accepted.

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